Dasatinib as Salvage Therapy for Steroid Refractory and Imatinib Resistant or Intolerant Sclerotic Chronic Graft-versus-Host Disease

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Sclerotic chronic graft-versus-host disease (scGVHD) is a severe form of this disease that resembles systemic sclerosis and has limited and disappointing treatment options. Tyrosine kinase inhibitors (TKI) targeting up-regulated profibrotic pathways, such as imatinib mesylate, have been proposed as a potential therapeutic approach for patients with scGVHD. Dasatinib, a second-generation TKI with a well-established safety and efficacy profile in chronic myeloid leukemia patients, who are refractory or intolerant to imatinib, has also shown potent antifibrotic effects. We present here the first direct clinical evidence, from 3 patients treated in a small single-center series, suggesting that dasatinib can be a therapeutic option for patients with severe scGVHD resistant or intolerant to imatinib. All patients achieved partial response, with improvement in scGHVD target organs severity, joint mobility, lung impairment, and deep fibrotic lesions. This clinical response has remained stable or continued to improve after a median of 22 months (20-25) on dasatinib treatment, with very good tolerance. In addition, corticosteroids could be discontinued or significantly reduced in all patients. This clinical evidence suggests that dasatinib could be a safe and effective alternative for scGVHD patients refractory to corticosteroids and resistant or intolerant to imatinib. Based on these preliminary findings, and in order to address appropriate patient selection, time of intervention, and choice of drug, future larger studies should more formally establish the efficacy and safety of second-generation TKI for the treatment of scGVHD.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is the major cause of late nonrelapse morbidity and mortality after allogeneic blood and marrow transplantation (alloBMT) [1,2]. Sclerotic chronic (sc) GVHD is 1 of the most severe forms of this disease, characterized by excess collagen production by activated fibroblasts, which resembles systemic sclerosis and is frequently refractory to standard treatment approaches [3]. Imatinib mesylate (IM) is a tyrosine kinase inhibitor (TKI) successfully used in patients with Bcr-Abl-positive leukemias [4,5]. In addition to its anti-Bcr-Abl effect, IM exerts a strong antifibrotic activity through inhibition of transforming growth factor-β and platelet-derived growth factor signaling pathways, which are key in the pathogenesis of fibrotic diseases like scGVHD [6-10]. Based on these data, several case reports and 2 initial series explored the use of IM as a novel therapeutic option for patients with scGVHD, and showed that up to 50% to 79% of these patients improve with this agent [11-14]. Nevertheless, one-third to one-half of patients with scGVHD treated with IM fail to respond or are intolerant to treatment.

Second-generation TKI have a greater inhibitory potency and a better tolerability profile than IM, and have been approved for the treatment of chronic myeloid leukemia (CML) patients who are refractory or intolerant to IM [15]. Dasatinib is a second-generation multikinase inhibitor, which, beyond its antileukemic effect, targets not only transforming

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growth factor-β and platelet-derived growth factor-receptor profibrotic signaling pathways, but also Src kinases, which play an important role in the development of experimental dermal fibrosis [16], and which have been shown to effectively inhibit the synthesis of extracellular matrix in both in vitro and in vivo models [17]. We hypothesized that dasatinib may be a therapeutic alternative for scGVHD. Here, we provide the first direct clinical evidence suggesting that dasatinib can indeed be a safe and effective therapeutic option for patients with severe scGVHD refractory to corticosteroids and resistant or intolerant to IM.

METHODS

We describe a single-center series of 3 patients with severe scGVHD who received salvage therapy with dasatinib after failing several previous lines of systemic therapy including corticosteroids and IM. Patient characteristics are summarized in Table 1. Hospital approval and informed consent for off-label use of the drug were obtained in all cases. Patients also signed and agreed for their data and images to be used to illustrate their clinical response in this paper. Dasatinib was started at a dose of 50 mg daily, and then escalated to 100 mg daily within 8 weeks in the absence of severe toxicity or intolerance. Adverse events were graded according to Common Terminology Criteria for Adverse Events, Version 3.0. Supportive care and antimicrobial prophylaxis and monitoring followed our standard protocols in keeping with international guidelines [18]. Diagnoses other than scGVHD, including infections and drug reactions, were previously excluded, and in all cases sclerodermatous features were histologically confirmed by skin biopsy (data not shown). Diagnosis and staging of scGVHD were assessed according to the National Institutes of Health Consensus Conference on cGVHD [19].

Before initiating dasatinib treatment, patients were carefully examined to determine their skin score, ulcer size, joint mobility, range of motion, Zubrod performance status, and evaluation of any other possible site involvement. Response to therapy was graded according to the criteria proposed by Couriel et al. [20]. Complete response was defined as resolution of all manifestations of cGHVD. Partial response was defined as at least 50% improvement in the affected site, as follows: for skin involvement, reduction ≥50% of body surface area involved by nonmoveable sclerosis, erythematous rash, and/or ulcers and improvement in Zubrod status by 1; for lung, sustained improvement in pulmonary function tests and/or steroid tapering by 50% without deterioration of pulmonary function. Additionally, joints and fascia partial response was defined as any improvement in range of motion and reduction in the National Institutes of Health score by 1 or more [19], without achieving complete response. Response in every affected site and global cGVHD score were prospectively evaluated at 3 monthly intervals from the start of treatment.

RESULTS AND DISCUSSION

All 3 patients treated with dasatinib in this series were resistant and/or intolerant to IM, and had additionally failed at least 3 previous systemic immunosuppressive lines, including refractoriness to first-line corticosteroids [2]. Before the start of dasatinib treatment, they all had severe sclerotic features including deep tissue sclerosis, joints contracture, severe mobility restriction, and functional impairment, as summarized in the scores and images in Table 1 and Figure 1. Patient #1 had a de novo scGVHD onset 9 months after a nonmyeloablative alloBMT. Despite initial treatment with prednisone (2 mg/kg) and cyclosporine A (CyA), and subsequent addition of mycophenolate mofetil (MMF), features of scGVHD continued to progress over the following months. She developed severe lung involvement with bronchiolitis obliterans confirmed in chest CT scans and pulmonary function tests that made her dependent on domiciliary-oxygen. Five months after the onset of scGVHD, IM (400 mg daily) was added to the treatment. While on IM, the features of scGVHD stabilized, but the patient remained oxygen dependent. After several months, the patient started experiencing gastrointestinal intolerance and grade 3-4 cytopenias requiring growth factor support, which would not allow escalation of the dose of IM. Eight months after initiation, IM was discontinued, based on intolerance and suboptimal response, and dasatinib was started. At this point the patient remained oxygen-dependent with no significant clinical improvement, and was still on CyA, MMF, and 1 mg/kg prednisone. Patient #2 had a quiescent scGVHD onset 5 months after an HLA-identical related-donor myeloablative alloBMT. An initial partial response was achieved with corticosteroids, CyA, and MMF. He subsequently received 10 doses of PUVA, which allowed tapering of corticosteroids first and CyA next, but had to be stopped as a result of skin intolerance. Two years later, ongoing sclerotic features progressed, with severe nail dystrophy, painful ulcers (Figure 1A), skin hypopigmentation, and nonscarring alopecia. Treatment with IM was tried for 3 months before switching to dasatinib for gastrointestinal intolerance and absence of clinical response. Patient #3 had de novo scGVHD onset 10 months after a myeloablative, unrelated donor alloBMT. Despite treatment with corticosteroids, CyA, and MMF, sclerotic features progressed along with generalized pruritus,

Table 1. Patient, Transplant, and scGVHD Characteristics and Response to Treatment with Dasatinib

	Patient #1		Patient #2		Patient #3	
Sex	Female		Male		Female	
Age at alloBMT	58		28		27	
Disease and status at alloBMT	First CR AML		First CR AML		First CR AML	
Conditioning regimen	RIC (Flu-Bu)		MAC (Cy-TBI)		MAC (Cy-TBI)	
GVHD prophylaxis	CyA, MTX		CyA, MTX		CyA, MTX, ATG*	
Donor relation; HLA matching	Related; 10/10		Related; 10/10		Unrelated; 10/10	
Stem cell source	PB		PB		PB	
Date of alloBMT	September 2007		April 2007		January 2008	
Acute GvHD	–		Cutaneous grade III on day + 42; Responsive to CS		–	
cGVHD onset, date (months from BMT)	De novo, June 2008 (9)		Quiescent, September 2007 (5)		De novo, November 2008 (10)	
Main cGVHD targets	Skin, joints, and lungs		Skin, joints, nails, hair, mouth, and eyes		Skin, joints, and nails	
Lines of systemic IS before IM	CyA, MMF, CS		CyA, MMF, CS, PUVA		CyA, MMF, CS	
Off-label indication for dasatinib use	IM intolerant (GI and cytopenias) and suboptimal response		IM intolerant (GI) and resistant to IM		Resistant to IM (progressive scGVHD)	
Start of dasatinib treatment	July 2009		December 2009		October 2009	
Months from alloBMT	22		32		21	
Months from scGVHD onset	13		26		11	
Months from start of IM	8		3		4	
Months on dasatinib (last follow up in August 2011)	25		20		22	
NIH SCORES	PRE	POST (12 months)	PRE	POST (6 months)	PRE	POST (12 months)
cGVHD overall score	Severe	Severe	Severe	Moderate	Severe	Moderate
Performance Status: Zubrod (Karnofsky)	3 (50%)	2 (70%)	2 (60%)	1 (80%)	2 (60%)	1 (90%)
Joints and fascia, NIH score	2	1	3	1	3	1
Decreased range of motion	Shoulders, elbow		Upper extremities		Left lower extremity, upper extremities	
Skin, NIH score	3 Generalized liquenoid changes; deep sclerosis (neck, axillas, forearms)	3 Improvement in sclerotic features and mobility	3 Deep slcerotic features (neck, axillas, hips)	2 Superficial sclerosis (not hidebound)	3 Deep sclerosis (arms, forearms, lower extremities) and facial hyperpigmentation	2 Superficial sclerosis (not hidebound). Changes in skin pigmentation in Figure 1.
Longest diameter of largest ulcer (location)	2 cm Back	No ulcer	3.6 cm Neck	No ulcer (see Figure 1)	No ulcer	No ulcer
Lung; NIH score (LFS)	3 (11)	2 (9)	0	0	0	0
Percent CS reduction		93%		100%		100%
Current prednisone dosage/day		10 mg		0		0
Status at last follow-up (August 2011)	Alive, CR 47 months after alloBMT		Alive, CR 52 m after AlloBMT		Alive, CR 43 m after AlloBMT	

PRE indicates scGVHD assessment according to National Institutes of Health (NIH) scoring before initiating; dasatinib treatment; POST, scGVHD assessment according to NIH scoring at best response (months after initiation of dasatinib treatment); IS, immunosuppression; LFS, lung function score (LFS = FEV1 score + DLCO score according to NIH; Scale 2 to 12); CS, corticosteroids; CR, complete remission; AML, acute myeloid leukemia; RIC, reduced intensity conditioning; Flu, fludarabine; Bu, busulphan; ATG, antithymocyte globulin; MAC, myeloablative conditioning; Cy, cyclophosphamide; TBI, total body irradiation; MTX, methrotexate; PB, peripheral blood; PUVA, Psolaren-UV-A therapy; GI, gastrointestinal.

*ATG (antithymocyte globulin; Thymoglobulin®): 2 mg/kg/day on days −3 to −1.

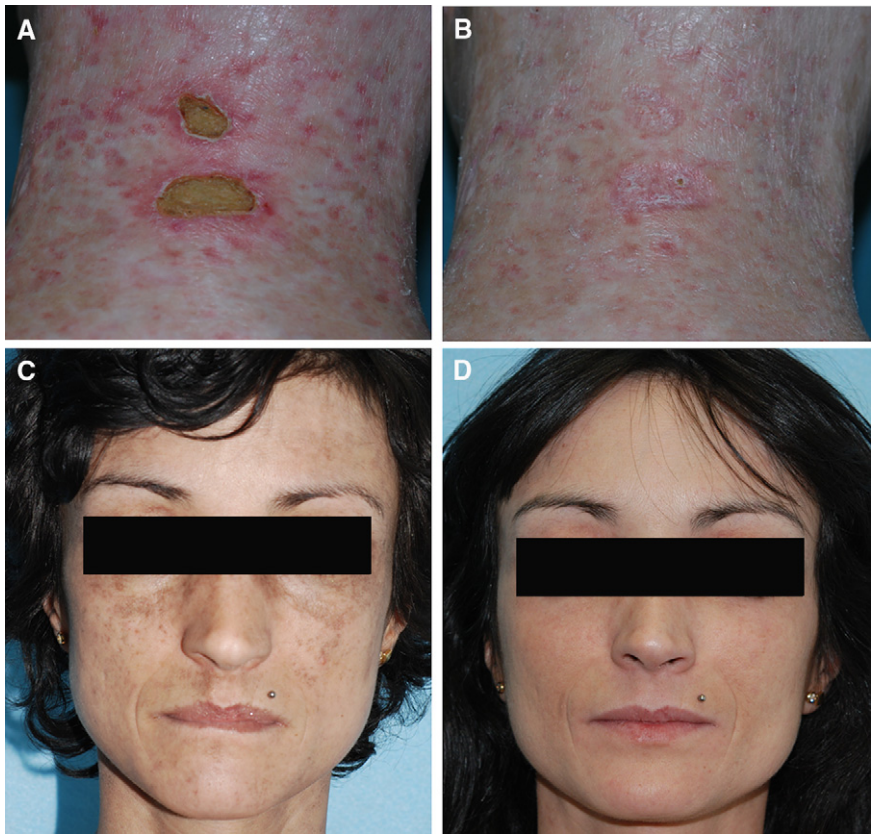

Figure 1. Response of skin scGVHD to dasatinib treatment. Patient #2: neck ulcers of 3.6 cm and 1.7 cm in diameter before initiating dasatinib treatment (A) and at 3 months (B). Patient #3: skin hyperpigmentation before initiating dasatinib treatment (C) and at 12 months (D).

skin ulcers from minor trauma, progressive skin hyperpigmentation (Figure 1C), and restriction of joint mobility, including severe left knee contracture lacking 20 degrees of extension, which caused a significant limitation in the range of motion of the left leg and the patient's capacity to walk normally. Disease continued to progress for 4 months of IM therapy before dasatinib was started.

Treatment change to dasatinib was tolerated well in all cases, allowing dose-escalation from 50 mg to 100 mg within 8 weeks, as scheduled. At the time of first response assessment, 3 months after the start of dasatinib, all patients had experienced disease response. Patients #1 and #2 had already achieved partial responses, with objective improvement in target organs severity, regression of deep sclerotic features in terms of body surface area involved by hidebound lesions, skin thickness, and ulceration (Figure 1B), along with improved joint motility and function. Patient #2, also showed resolution of photophobia and improvement of his dry eye symptoms, which allowed discontinuation of his eyedrops, as well as disappearance of mouth mucosal ulcers and improvement of his sensitive and dry mouth symptoms. Patient #1 also showed an initial improvement of her pulmonary involvement, and by 12 months of dasatinib treatment she became oxygen-independent at rest while undergoing a greater than 90% reduction of her initial corticosteroid dose (Table 1). After 3 months of dasatinib therapy, patient #3 achieved initial stabilization of her sclerotic features, which had been in frank progression under IM. Six months later, she started progressive clinical and functional improvement. By 12 months, she achieved a partial response, including resolution of her hyperpigmented skin lesions (Figure 1D) and full normalization of her left lower extremity range of motion, becoming again able to walk normally, with her functional disability almost normalized (Table 1).

At the most recent follow-up, patients have been on dasatinib for scGVHD for a median of 22 months (20-25). The safety of dasatinib in this setting has remained very good, with no observed grade 3-4 adverse events, and minor grade 1-2 adverse events (Table 2), which did not require treatment discontinuation or dose adjustment. All patients are alive and in complete remission of their primary disease at a median of 47 months after transplantation (43-52). Patient #1 remains on a stable partial response of her scGVHD on dasatinib and with her corticosteroid dose down to 0.16 mg/kg of oral prednisone. Patients #2 and #3

Table 2. Laboratory Findings and Adverse Events during Treatment with Dasatinib in Patients with scGVHD

	Patient #1					Patient #2					Patient #3				
	Pre	1m	3m	12m	Last FU	Pre	1m	3m	12m	Last FU	Pre	1m	3m	12m	Last FU
Hemoglobin (g/L)	127	124	122	125	127	127	124	95§	98§	99§	114	117	111	120	111
Platelets ($\times 10^9$/L)	301	221	355	303	322	251	218	300	269	328	286	315	330	310	306
Leukocytes ($\times 10^9$/L)	9.7	8.3	4.6	8.8	5.6	8.9	8.8	7.4	7.8	6.5	9.6	10.3	9.8	7.2	7.1
Neutrophils ($\times 10^9$/L)	4.5	4.7	2.3	5	3.8	6.5	6.8	5.8	4.9	4.6	5.5	6.5	5.9	3.0	4.3
AST (ukat/L)	0.44	2.02¶	0.7§	0.61§	0.46	0.4	0.45	0.28	0.25	0.43	0.41	0.37	0.4	0.34	0.47
ALT (ukat/L)	0.49	2.16¶	0.48	0.47	0.43	0.45	0.37	0.14	0.16	0.25	0.4	0.44	0.33	0.38	0.42
Bilirubin (μmol/L)	10	4	7	5	6	5	3	2	2	3	5	2	4	3	5
GGT (U/L)	24	138¶	120¶	105¶	114¶	59§	64§	42§	60§	28	71§	127¶	101¶	73§	43§
A. Phosphatase (ukat/L)	1.1	3.3§	2.1§	2.2§	1.4	1.2	1.1	0.9	0.87	1.4	1.2	2.2§	2.4§	3§	2.1§
Creatinine (μmol/L)	83	92	77	85	88	95	135§	150§	133§	109	55	64	51	58	83

Pre indicates before start of dasatinib treatment; 1m, 3m, 12m, number of months from start of dasatinib treatment; FU, follow-up; Adverse events graded according to Common Terminology Criteria for Adverse Events, Version 3.0, as grade 1 (§) and grade 2 (¶). There were no adverse events grades higher than 2.

are both off corticosteroids and continue to show further clinical improvement.

First- and second-generation TKI offer an exciting new avenue for treatment of patients with severe scGVHD. Their well-established safety profile is particularly suitable for such heavily immunosuppressed patients, many of whom die from the associated susceptibility to infections induced by multiple lines of immunosuppressive drugs [1]. Breccia et al. [21] have reported indirect evidence in a patient treated with low-dose dasatinib for a CML relapse after haploidentical BMT: that the drug may have an immunomodulatory effect over hepatic cGVHD. Our experience in alloBMT recipients for Bcr-Abl-negative leukemias provides the first direct clinical evidence to suggest that treatment with dasatinib may indeed be a safe and effective therapeutic alternative for patients with severe scGVHD refractory to standard therapy. Our 3 cases improved their scGVHD severity score in target organs, remarkably including severe lung impairment and joint restrictions. This clinical response has remained stable or continued to improve in all 3 cases after a median of nearly 2 years on dasatinib treatment, with good tolerance. This allowed us to discontinue corticosteroids in 2 cases and to reduce to <10% of the initial dose in the third case. The complexity of the pathophysiology underlying scGVHD and our limited understanding of the mechanisms of action and the factors predicting success of the use of TKI in this setting is emphasized by an interesting case reported by Pulanic et al. [22] where an alloBMT recipient developed severe scGVHD while on treatment with dasatinib for persistence of residual CML after transplant. On the other hand, although dasatinib was first approved for CML only in patients who were resistant or intolerant to IM, recent studies have shown that first-line dasatinib treatment does induce significantly higher and faster response rates than IM [23]. Based on this evidence in CML, one may hypothesize that dasatinib may be a preferable first-line TKI to IM also for scGVHD, in particular, considering the severity and high rates of morbidity and mortality of this disease. Our preliminary experience suggests that dasatinib is a safe and effective therapeutic option for patients with severe scGVHD refractory to corticosteroids and resistant or intolerant to IM. Despite these early responses and encouraging findings in our series, a noncomparative design cannot formally exclude, for instance, disease evolution over time rather than continuous effect of dasatinib therapy to be responsible for longer term improvement. Many additional questions remain, and future larger studies should more formally establish the efficacy and safety of second-generation TKI for the treatment scGVHD, as well as help us address appropriate patient selection, optimal time of intervention, and choice of drug.

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